Translation

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference PCT99/19 PH	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/EP00/09392	International filing date (*day/month/year*) 26 September 2000 (26.09.00)	Priority date (*day/month/year*) 30 September 1999 (30.09.99)
International Patent Classification (IPC) or national classification and IPC A61K 31/57		
Applicant VIATRIS GMBH & CO. KG		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 6 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 2 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☒ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
21 February 2001 (21.02.01)	15 January 2002 (15.01.2002)
Name and mailing address of the IPEA/EP Facsimile No.	Authorized officer Telephone No.

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/EP00/09392

I. Basis of the report

1. With regard to the **elements** of the international application:*

☐ the international application as originally filed

☒ the description:

pages 1-13 , as originally filed

pages _____ , filed with the demand

pages _____ , filed with the letter of _____

☒ the claims:

pages _____ , as originally filed

pages _____ , as amended (together with any statement under Article 19

pages _____ , filed with the demand

pages 1-9 , filed with the letter of 29 October 2001 (29.10.2001)

☐ the drawings:

pages _____ , as originally filed

pages _____ , filed with the demand

pages _____ , filed with the letter of _____

☐ the sequence listing part of the description:

pages _____ , as originally filed

pages _____ , filed with the demand

pages _____ , filed with the letter of _____

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.
These elements were available or furnished to this Authority in the following language _____ which is:

☐ the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).

☐ the language of publication of the international application (under Rule 48.3(b)).

☐ the language of the translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

☐ contained in the international application in written form.

☐ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. ☐ The amendments have resulted in the cancellation of:

☐ the description, pages _____

☐ the claims, Nos. _____

☐ the drawings, sheets/fig _____

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).**

* *Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rule 70.16 and 70.17).*

** *Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.*

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

national application No.
PCT/EP 00/09392

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	1-10	YES
	Claims		NO
Inventive step (IS)	Claims		YES
	Claims	1-10	NO
Industrial applicability (IA)	Claims	1-10	YES
	Claims		NO

2. Citations and explanations

1. a) The following documents cited in the international search report are referred to:

D1: RESPIRATORY MEDICINE, vol. 91, no. 10, 1997, pages 587-591
D2: THORAX, vol. 52, no. 6, 1997, pages 535-539
D3: US-A-5 830 490
D4: WO-A-00/28979

b) According to D1, long-acting β_2 agonists, for example, **salmeterol and formoterol**, are bronchospasmolytics which, used as **inhalations** in **asthma treatment**, should always be given in combination with **corticosteroids**. Short-acting β_2 agonists, for example, **salbutamol**, may be given additionally (see abstract; page 587 'Introduction'; page 589, right-hand column, paragraph 4; page 590 'Conclusion'). The corticosteroids indicated include **beclomethasone dipropionate, budesonide and fluticasone propionate** (see page 588, left-hand column, lines 1-2; page 589, right-hand column, line 19). Loteprednol is not mentioned.

c) The clinical study described in D2 shows that the symptoms of **asthma patients** are improved on **inhalation** of the long-acting β_2 agonist **formoterol** in addition to **inhaled** corticosteroids (see abstract; page 536 'Subjects'; page 538 'Discussion'). Loteprednol is not mentioned. D2 does not specify the corticosteroids used.

d) D3 describes a system which optimizes the combined use of an aerosol and an oral drug. The system may be used to treat, for example, **rhinitis**, **bronchitis** and **asthma** (see abstract and column 4, line 7). **Corticosteroids**, for example, beclomethasone, and **bronchodilatory adrenergic agonists**, for example, **albuterol**, may be used, for example, topically in the respiratory tract in aerosol form (see Example 4). The compounds loteprednol, salbutamol, reproterol, salmeterol and formoterol are not mentioned.

2. Novelty

a) D1-D3 do not disclose pharmaceutical preparations for inhalation comprising, separately or in combination, loteprednol or a pharmaceutically tolerable ester thereof and at least one β_2-adrenoceptor agonist. Therefore, **the subject matter of independent Claim 1 and dependent Claims 2-6 is novel** within the meaning of PCT Article 33(2).

b) 2.a) likewise applies to **Claims 7, 8 and 9**, which all pertain to a combination of loteprednol and a β_2-adrenoceptor agonist (PCT Article 33(2)).

3. Inventive step

According to D1 (cf. 1.b)), which is considered to represent the closest prior art with respect to the subject matter of Claim 1, long-acting β_2 agonists, for example, **salmeterol and formoterol**, are bronchospasmolytics which, used as **inhalations** in **asthma treatment**, should always be given in combination with **corticosteroids**. Short-acting β_2 agonists, for example, **salbutamol**, may be given additionally. The corticosteroids indicated include **beclomethasone dipropionate, budesonide and fluticasone propionate**.

The subject matter of Claim 1 differs from D1 in **the use** of the "soft" steroid **loteprednol** and/or a pharmaceutically tolerable ester thereof **as a corticosteroid**.

The problem addressed by the present invention may therefore be seen to consist in the treatment of **bronchial asthma**.

With D1 as the point of departure, whether viewed in isolation or in conjunction with one of the above-indicated citations, a person skilled in the art could not deduce that **loteprednol, a "soft" steroid which has apparently not been previously used in asthma treatment**, is efficacious in combination with a β_2 agonist in treating asthma.

However, the applicant has not adequately substantiated the claimed use of the active substances in treating **allergies** and **diseases of the**

airways. According to the description, the active substances are given as an inhalation (see page 3, last paragraph). In *in vivo* studies the active substances were also introduced **directly into the lung** (see page 5). The preparations described in the present application were evidently developed for the treatment of **bronchial asthma** (see page 4, line 4, and pages 4-5).

It is not possible to accept that the active substances in the present application are efficacious in treating **any type of allergy** (for example, contact allergies) or **all diseases of the airways** and are suitable for **further uses**.

A concluding report on inventive step (PCT Article 33(3)) cannot, therefore, be established for the subject matter of Claim 1, dependent Claims 2-6 and Claims 7-9.

4. Industrial applicability

The PCT Contracting States do not have uniform criteria for assessing the industrial applicability of Claims 1-7 and 9 in their present form. Patentability may depend of the wording of the claims. The EPO, for example, does not recognize the industrial applicability of claims to the medical use of a compound; it does, however, allow claims to the first medical use of a known compound or to the use of such a compound in the manufacture of a drug for a new medical application.

VI. Certain documents cited

1. Certain published documents (Rule 70.10)

Application No. Patent No.	Publication date *(day/month/year)*	Filing date *(day/month/year)*	Priority date (valid claim) *(day/month/year)*
WO 00/28979 (D4)	25 May 2000 (25.05.2000)	10 November 1999 (10.11.1999)	13 November 1998 (13.11.1998)

2. Non-written disclosures (Rule 70.9)

Kind of non-written disclosure	Date of non-written disclosure *(day/month/year)*	Date of written disclosure referring to non-written disclosure *(day/month/year)*

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: VI.2

D4 describes the use in dry powder formulations for inhalation of magnesium stearate in order to improve storage stability. The formulations preferably contain a **corticosteroid**, for example, **loteprednol etabonate**, in combination with a **beta-mimetic drug**, for example, **formoterol fumarate**, **formoterol tartrate** or **salmeterol xinafoate** (see Claims 1 and 15). D4 does not address the treatment of allergies or diseases of the airways.

Patent claims

1. Pharmaceutical preparation comprising, separately or together, an efficacious amount of (i) loteprednol or a pharmaceutically tolerable ester thereof and (ii) at least one β_2 adrenoceptor agonist for simultaneous, sequential or separate administration by inhalation in the treatment of airway disorders in mammals.

2. Pharmaceutical preparation according to claim 1, characterized in that the pharmaceutically tolerable ester of loteprednol is loteprednol etabonate.

3. Pharmaceutical preparation according to claim 1 or 2, characterized in that the β_2 adrenoceptor agonist is selected from the group consisting of salbutamol, reproterol, salmeterol, formoterol and their pharmaceutically tolerable salts.

4. Pharmaceutical preparation according to one of claims 1 to 3, characterized in that it contains (i) loteprednol and (ii) formoterol.

5. Pharmaceutical preparation according to one of claims 1 to 3, characterized in that it contains (i) loteprednol and (ii) salmeterol.

6. Pharmaceutical preparation according to one of claims 1 to 3, characterized in that it contains (i) loteprednol and (ii) reproterol.

7. Medicament for the treatment of allergies and/or airway disorders, comprising an efficacious amount of (i) loteprednol and (ii) at least one β_2 adrenoceptor agonist, if appropriate together with customary excipients or vehicles, for simultaneous, sequential or separate administration.

8. Process for the production of a medicament for the treatment of allergies and/or airway disorders, comprising the active compound loteprednol and at least one β_2 adrenoceptor agonist, characterized in that loteprednol and the β_2 adrenoceptor agonist or the β_2 adrenoceptor agonists are mixed individually or together, if appropriate together with customary excipients or vehicles, and the mixture thus obtained is converted into suitable administration forms.

9. Use of the combination of loteprednol and at least one β_2 adrenoceptor agonist for the production of a medicament for the simultaneous, sequential or separate treatment of allergies and/or airway disorders.